IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Manne Satyanarayana REDDY et al. Art Unit: 1625

Application No.: 10/647,449 Examiner: C. C. Chang

Filed: August 25, 2003

For: POLYMORPHIC FORMS OF (S)-REPAGLINIDE AND THE PROCESSES FOR PREPARATION THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

BRIEF ON APPEAL

Further to the Notice of Appeal filed on July 6, 2006 for the subject application, a brief in support of the appeal is now submitted. Submission of a brief in support of the appeal is due by September 6, 2006. Accordingly, this brief is being timely filed.

1. Real Party in Interest

The real parties in interest are Dr. Reddy's Laboratories Limited and Dr. Reddy's Laboratories, Inc., assignees of the application from the inventors/appellants.

2. Related Appeals and Interferences

There are no appeals or interferences that are related to this appeal, or which will affect or have a bearing on this appeal.

3. Status of the Claims

Claims 1-57 were finally rejected in an Office Action mailed on March 6, 2006, although claims 3, 39, 49, 52 and 55 were previously canceled in an Amendment submitted on December 1, 2005. Accordingly, claims 1-2, 4-38, 40-48, 50, 51, 53, 54, 56 and 57 are the subject of this appeal.

4. Status of Amendments

A response was filed on April 25, 2006, subsequent to final rejection. No claims were amended, canceled or added. The Examiner indicated in an Advisory Action mailed May 26, 2006, that the response did not place the application in condition for allowance. All amendments have been entered.

5. Summary of Claimed Subject Matter

The claimed subject matter encompasses crystalline and amorphous forms of the drug compound (S)-repaglinide.

Independent claim 1 is directed to a crystalline Form III of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 1 of the instant specification. (Instant specification, pages 14-15, ¶¶ 0049-0050.)

Independent claim 8 is directed to a composition comprising (S)-repaglinide as a solid, wherein at least 80% by weight of said solid (S)-repaglinide is in crystalline Form III having an X-ray powder diffraction pattern, expressed in terms of 2 theta angles, that includes five or more peaks selected from the group consisting of 4.44 ± 0.09, 6.81 ± 0.09, 7.80 ± 0.09, 9.28 ± 0.09, 11.09 ± 0.09, 11.89 ± 0.09, 12.92 ± 0.09, 13.46 ± 0.09, 14.34 ± 0.09, 15.77 ± 0.09, 16.24 ± 0.09, 17.08 ± 0.09, 18.06 ± 0.09, 18.75 ± 0.09, 19.25 ± 0.09, 19.59 ± 0.09, 19.99 ± 0.09, 20.34 ± 0.09, 21.18 ± 0.09, 21.96 ± 0.09, 22.18 ± 0.09, 22.58 ± 0.09, 23.24 ± 0.09, 23.77 ± 0.09, 24.08 ± 0.09, 25.02 ± 0.09, 25.31 ± 0.09, 25.78 ± 0.09, 26.67 ± 0.09, 27.39 ± 0.09, 28.03 ± 0.09, 30.26 ± 0.09, 35.50 ± 0.09, and 38.74 ± 0.09 degrees. (Instant specification, page 15, ¶ 0052; pages 17-18, ¶ 0056.)

Independent claim 15 is directed to a pharmaceutical composition formed by combining: a) a crystalline Form III of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 1 of the instant specification; and b) a pharmaceutically acceptable carrier or diluent. (Instant specification, pages 14-15, ¶¶ 0049-0050; page 21, ¶ 0062.)

Independent claim 19 is directed to a process for preparing a crystalline Form III of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 1 of the instant specification, the process comprising: (a) providing a solution of (S)-repaglinide in a haloalkane solvent; (b) contacting said solution with a C_5-C_{10} aliphatic or alicyclic hydrocarbon anti-solvent thereby forming a precipitate; and (c) isolating the precipitate to provide the crystalline Form III of (S)-repaglinide. (Instant specification, pages 18-19, ¶ 0058.)

Independent claim 36 is directed to a process for preparing a crystalline Form III of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 1 of the instant specification, the process comprising: (a) dissolving (S)-repaglinide in dichloromethane to form a solution; (b) adding petroleum ether to the solution to form a precipitate; and (c) isolating the precipitate to provide the crystalline Form III of (S)-repaglinide. (Instant specification, pages 14-15, ¶¶ 0049-0050; pages 19-20, ¶ 0059.)

Independent claim 38 is directed to an amorphous form of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 4 of the instant specification. (Instant specification, page 20, ¶¶ 0060.)

Independent claim 40 is directed to a process for making an amorphous form of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 4 of the instant specification, the process comprising: (a) providing a solution of (S)-repaglinide in a lower alcohol; (b) cooling said solution so that a solid mass separates; and (c) isolating said separated solid mass to provide the amorphous form of (S)-repaglinide. (Instant specification, pages 20-21, ¶¶ 0060-0061.)

Independent claim 50 is directed to a process for preparing a crystalline Form II of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Table 3 of the instant specification, the process comprising: (a) providing a solution of (S)-repaglinide in an aromatic hydrocarbon solvent, with the proviso that said solvent does not include petroleum ether; (b) cooling said solution to separate a solid mass; and (c) isolating said solid mass to provide the crystalline Form II of (S)-repaglinide. (Instant specification, pages 9-10, ¶¶ 0037-0040.)

The dependent claims are directed to various embodiments of the disclosed compounds, compositions and processes.

A copy of the appealed claims is appended hereto, beginning at page 15.

6. Grounds of Rejection to be Reviewed on Appeal

A. Whether claims 38 and 40-48 are anticipated under 35 U.S.C. § 102(b) by Grell et al (U.S. Pat. No. 5,312,924; "Grell I").

B. Whether claims 1, 34 and 35 are anticipated under 35 U.S.C. § 102(b) by Grell I.

C. Whether claims 1, 2, 4-38, 50, 51, 53, 54, 56 and 57 are unpatentable under 35 U.S.C. § 103(a) over Grell I in view of Grell et al. (*J. Med. Chem.*, 1998, 41:5219-5246; "Grell II") and Brittain, ed. (Polymorphism in Pharmaceutical Sciences, 1999, pp. 179-79, 185, 219; "Brittain").

D. Whether claims 8-18 are invalid under 35 U.S.C. § 112, first paragraph for failing to comply with the written description and enablement requirements.

7. Argument

A. Rejection of Claims 38 and 40-48 Under 35 U.S.C. § 102(b)

Claims 38 and 40-48 stand finally rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Grell I. According to the Examiner in the Office Action mailed July 15, 2005, column 23, lines 15-17 of Grell I discloses the non-

crystalline solid after evaporation of solvent ethanol. This solid, according to the Examiner, is amorphous and the process is the same as that claimed.

It has long been the law that anticipation can properly be held only where a prior art document teaches each and every limitation of the rejected claim, either expressly or inherently. *See Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *See In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981). The examiner must provide some evidence or scientific reasoning to establish the reasonableness of his or her belief that the functional limitation is an inherent characteristic of the prior art. *See Ex parte Skinner* 2 USPQ2d 1788, 1789 (BPAI 1986).

Here, claims 38 and 40-48 are directed to amorphous (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 4 of the instant specification. Column 23, lines 15-17 of Grell I is not even directed to S-repaglinide, (S)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid, but rather to the compound 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl}-aminocarbonylmethyl]-benzoic acid. As such, this disclosure of Grell I cannot anticipate claims 38 and 40-48 of the instant application.

For the sake of completeness, Appellants point out that other portions of Grell I appear to disclose the preparation of (S)-repaglinide. None of these disclosures, however, teach amorphous (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 4 of the instant specification. For example, Example 3 at column 85, lines 40-56 discloses the preparation of (S)-repaglinide from ethyl (S)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoate, whereby the high melt crystalline form of (S)-repaglinide is obtained. Similarly, Example 11 at column 89, lines 46-59 discloses the preparation of (S)-repaglinide from tert.butyl (S)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoate, but again the high melt crystalline form of (S)-repaglinide is obtained. Example 106

at column 58, line 35 to column 59, line 5, Example 10 at column 89, lines 26-45 and Example 12, column 89, line 60 to column 90, line 14, each disclose the preparation of crystalline (S)-repaglinide involving evaporation steps, but the Examiner has not provided any evidence or scientific reasoning to establish that the evaporation product is amorphous (S)-repaglinide, let alone amorphous (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 4 of the instant specification.

Furthermore, claims 40-47 are directed to a process for making an amorphous form of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 4, the process comprising: (a) providing a solution of (S)-repaglinide in a lower alcohol; (b) cooling said solution so that a solid mass separates; and (c) isolating said separated solid mass to provide the amorphous form of (S)-repaglinide. In contrast, the above-described passages from Grell I all involve isolation of crystalline (S)-repaglinide from solution. Accordingly, Appellants submit that claims 38 and 40-48 are not anticipated by Grell I under § 102(b), and the rejection should not be sustained.

B. Rejection of Claims 1, 34 and 35 Under 35 U.S.C. § 102(b)

Claims 1, 34 and 35 stand finally rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Grell I. According to the Examiner in the Office Action mailed March 6, 2006, the instant product and the product of Grell I are essentially the same based on IR spectra (comparing Figure 4 of the instant specification with Figures 2 and 3 of Grell I). The Examiner states that no evidence exists in the record showing that the instant crystalline form and forms A, B and C of Grell I are different, especially in view of the margin of error for X-ray diffraction patterns.

Appellants take exception with the Examiner's characterization of the IR spectra at issue. The IR spectra from the instant application (shown in Figure 3, not Figure 4 as the Examiner stated) was obtained on solid crystalline Form III of (S)-repaglinide. (*See* instant specification, page 17, ¶ 0055.) In contrast, the IR spectra shown in Figures 2 and 3 of Grell I were obtained on racemic repaglinide

in methylene chloride solution. (*See* Grell I, col. 32, lines 15-68.) Thus, contrary to the Examiner's contention, the IR spectra do not demonstrate that instant product and the product of Grell I are essentially the same.

Furthermore, evidence does exist in the record, in the form of X-ray diffraction patterns disclosed in the instant specification, clearly demonstrating that that the instant and prior art products are different. Table 6 shows the X-ray diffraction peaks for crystalline Form III of (S)-repaglinide, while Tables 1 and 2 show the X-ray diffraction peaks for (S)-repaglinide re-precipitated from racemic repaglinide using the solvent systems described in Grell I. Even a cursory inspection of the data in these tables reveals that the X-ray diffraction pattern for crystalline Form III of (S)-repaglinide is distinctly different from that for (S)-repaglinide obtained from the solvent systems described in Grell I. In addition, the instant specification lists the melting point of crystalline Form III of (S)-repaglinide as 80-84° C (*see* instant specification, pages 25-27, ¶¶ 0079-0083) while Grell I lists the melting points for two crystalline forms of (S)-repaglinide as 130-131° (high-melting form) or 99-101° C (low-melting form) (*see* Grell I, col. 85, ln. 40 to col. 86, ln. 11). Appellants submit that such evidence indicates that crystalline Form III of (S)-repaglinide recited in claims 1, 34 and 35 is patentably distinct from the prior art products disclosed in Grell I, and the § 102(b) rejection should not be sustained.

C. Rejection of Claims 1, 2, 4-38, 50, 51, 53, 54, 56 and 57 Under 35 U.S.C. § 103(a)

Claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 stand finally rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Grell I in view of Grell II and Brittain.[1] According to the Examiner in the Office Action mailed March 6, 2006, even assuming that the X-ray diffraction pattern is different from the product of the art, it is, in the strictest sense, the same pure substance of the prior art, i.e., *prima facie* obvious unless some form of unobviousness can be provided. The

[1] For purposes of this Appeal Brief, Appellants presume that the Examiner intended to include claim 38 in the § 103(a) rejection.

Examiner states in the office Action mailed July 15, 2005, that the employment of different solvents in the crystallization process are art recognized variations for obtaining different forms.

The standards for making an obviousness rejection are summarized in MPEP § 706.02(j) as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claims 1, 2 and 4-38 are directed to crystalline Form III of (S)-repaglinide. As discussed above with respect to the second § 102(b) rejection, Grell I discloses crystalline forms of (S)-repaglinide having solid state characteristics (e.g., X-ray diffraction pattern, IR spectra, melting point) distinctly different from that of Form III. Similarly, Grell II discloses two forms of (S)-repaglinide in its Table III having melting points similar to the high-melt and low-melt forms of Grell I, and thus different from that of Form III. Brittain merely teaches that solid compounds may exist in different crystalline forms or polymorphs (but does not specifically mention (S)-repaglinide), and thus adds nothing over the Grell references. There is no teaching, or even a suggestion, in the cited references that (S)-repaglinide exists in other polymorphic forms, let alone Form III disclosed and claimed in the instant application. This alone is enough to overcome the Examiner's obviousness rejection. *See Ex parte Havens*, Appeal No. 2001-0091 for Application No. 08/732,254, now US 6,452,007 B1 (BPAI 2001) ("The examiner's obviousness rejection seems to suffer the same infirmity as her anticipation rejection . . . The examiner has provided no evidence or convincing

reason why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the specific S and T crystal forms that are the subject of the instant claims.") (emphasis added).

Contrary to the Examiner's position, the proper test for obviousness in this case is not whether the existence of (S)-repaglinide polymorphs is suggested by the prior art, but whether it would have been obvious to make the particular (S)-repaglinide form claimed in the instant application based on the prior art:

> The law of § 103 requires quite a different inquiry from that conducted by the ALJ. Thee correct inquiry is not whether the Bouzard monohydrate [polymorph] could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether it would have been obvious to make the Bouzard monohydrate, based on the prior art.

Bristol-Myers Co. v. U.S. Int'l Trade Comm'n, 892 F.2d 1050, (Fed. Cir. Dec. 8, 1989) (emphasis added).

Here, the references cited by the Examiner suggest at most the possibility of other (S)-repaglinide polymorphs. The Examiner has pointed to nothing in the cited references, however, that would suggest to one skilled in the art the particular form claimed in the instant application, or a method for its preparation. In fact, Brittain, p. 185, cited by the Examiner, states that "[t]he developmental scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found." Because of this unpredictability, Appellants submit that no *prima facie* case for obviousness of claims 1, 2 and 4-38 under § 103(a) has been made out, and the rejection should not be sustained. *See Ex parte Andrews*, Appeal No. 2002-0941 of Application No. 09/166,445, now US 6,713,481 B1 (BPAI 2003) ("[T]he examiner has not adequately explained how a person having ordinary skill would have been led from 'here to there,' i.e., from the [prior art] compound having formula I to the crystalline polymorph form I recited in claims 1 through 5."); and *Ex parte Portmann*, Appeal No. 2003-1199 for Application No. 09/125,329, now US 6,740,669 B1(BPAI 2003) (same).

At page 4 of the Office Action mailed July 15, 2005, the Examiner states in support of the § 103(a) rejection:

> [A]s set forth by the court in In re Cofer 148 USPQ 268, Ex parte Hartop 139 USPQ 5252, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained thereform, are unpatentable. The instant claims are drawn to the ***same pure substance*** as the prior art that only has *different arrangements and or different conformations of the molecule*. Mere difference in physical property is well known conventional variation for the same pure substance . . . i.e. prima facie obvious. (Emphasis in original.)

In doing so, the Examiner appears to be taking the position that new polymorphs are *per se* unpatentable over the originally identified compound or previously identified polymorphs of the same compound. Such a rule, however, is inconsistent with the law on obviousness. *See Ex parte Andrews*, *supra* (quoting *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) ("The use of *per se* rules flouts § 103 and the fundamental case law applying it. . . [R]eliance on *per se* rules of obviousness is legally incorrect and must cease."); *Ex parte Portmann*, *supra* (same). Accordingly, courts have consistently found new polymorphs to be patentable over other forms of the same compound. *See, e.g.*, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043 (Fed. Cir. 1995) (ranitidine form 2 patentable over form 1); *Bristol-Myers Co. v. U.S. Int'l Trade Comm'n*, *supra* (Bouzard cefadroxil monohydrate patentable over other cefadroxil forms); *Silvestri v. Grant*, 496 F.2d 593 (CCPA 1974) (ampicillin B patentably distinct from ampicillin A); *In re Irani*, 427 F.2d 806 (CCPA 1970) (crystalline anhydrous ATMP patentable over amorphous ATMP); *In re Cofer*, 354 F.2d 664 (CCPA 1966) (crystalline 2,2-B patentable over liquid 2,2-B).

The Examiner's reliance on *In re Cofer* and *Ex parte Hartop* are misplaced in this instance. *In re Cofer* actually held the claimed crystalline 2,2-bis compound patentable because:

> [T]he board failed to address . . . whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining the structure or form. (Emphasis added.)

354 F.2d at 668. The *Cofer* court addressed the *Ex parte Hartop* decision, which had been relied upon by the board in finding the claimed crystalline 2,2-bis unpatentable:

> We think examination of the decisions relied on . . . in *Hartop* will demonstrate that the materials involved therein were found unpatentable where the alleged difference in form or purity of those substances was either disclosed or inherent therein. (Emphasis added.)

Id. at 667. Here, as discussed above, the references cited by the Examiner neither disclose or suggest the particular (S)-repaglinide form disclosed and claimed in the instant application.

The Board of Patent Appeals & Interferences has recently cautioned against the reliance on *Ex parte Hartop* in polymorph cases. As stated in *Ex parte Gala*:

> The examiner relies heavily on this proposition of law set forth in *Ex parte Hartop* . . : "[m]erely changing the form, purity or another characteristic of an old product, the utility remaining the same as that for the old product, does not render the claimed product patentable." According to the examiner, polymorph form 2 loratadine is merely another form of an old product (polymorph form 1 loratadine) and both forms possess the same utility. Accordingly, the examiner concludes that applicants' claims, reciting polymorph form 2 loratadine, are unpatentable. We disagree. Here, we invite attention to *In re Cofer* . . . , where the court substantially discredited PTO reliance on the above-quoted proposition of law in *Hartop*. Like the situation presented in *Cofer*, the examiner in this case has not adequately established that the prior art (1) suggests the polymorph form 2 of loratadine; or (2) discloses or renders obvious a method for making the polymorph form 2 of loratadine. (Emphasis added.)

Appeal No. 2001-0987 for Application No. 09/169,109, now US 6,335,347 B1 (BPAI 2002); *see also Ex parte Andrews*, *supra* ("[T]he principal of law enunciated in *Ex parte Hartop* . . . has been substantially discredited in *In re Cofer* . . ."); *Ex parte Portmann*, supra (same).

According to the Examiner, Appellants must provide evidence which demonstrates that the claimed compound exhibits an unexpected advantage over the prior art product. Appellants respectfully submit that such evidence need not be provided because a *prima facie* case of obviousness has not been made out under the proper test described above. The CCPA in *In re Grose* specifically rejected the application of the law of structural obviousness, and hence a requirement for a showing of unexpected properties, when analyzing the patentability of new solid state forms:

> No reason exists for applying the law relating to structural obviousness of those compounds which are homologs or isomers of each other to this case. . . . A zeolite, like those of the instant case, is not a compound which is a homolog or isomer of another, but is a mixture of various compounds related to each other by a particular crystal structure. Moreover, no other chemical theory has been cited as a basis for considering appellants' zeolite as prima facie obvious in view of [the prior art] zeolite R.

592 F.2d 1161, 1167-68 (CCPA 1979).

Accordingly, Appellants submit that claims 1, 2 and 4-38 are not *per se* unpatentable under § 103(a), and the rejection should not be sustained.

Regarding claims 50, 51, 53, 54, 56 and 57, these claims are directed to a process for preparing a crystalline Form II of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Table 3, the process comprising: (a) providing a solution of (S)-repaglinide in an aromatic hydrocarbon solvent, with the proviso that said solvent does not include petroleum ether; (b) cooling said solution to separate a solid mass; and(c) isolating said solid mass to provide the crystalline Form II of (S)-repaglinide.

According to the Examiner the employment of different solvents in the crystallization process are art recognized variations for obtaining different forms. Again, however, the proper test for obviousness is not whether the use of different solvents could result in different forms, but whether it would have been obvious to make a <u>particular</u> form using the claimed process based on the prior art. Although crystalline Form II of (S)-repaglinide is acknowledged by the

Appellants to be a prior art form, the Examiner has pointed to nothing in the prior art that would suggest Appellants' claimed process for obtaining Form II, or a reasonable expectation of success for any other method. As discussed above, Brittain describes the polymorph field as unpredictable. Appellants, and appellants alone, disclose that crystalline Form II of (S)-repaglinide can be prepared from a solvent containing an aromatic hydrocarbon but does not include petroleum ether. (*See* instant specification, page 9, ¶ 0037.) Nothing in the prior art suggests that such a process would yield crystalline Form II of (S)-repaglinide. As such, Appellants submit that no *prima facie* case for obviousness of claims 50, 51, 53, 54, 56 and 57 under § 103(a) has been made out, and the rejection should not be sustained. *See Ex parte Gala*, *supra* ("Applicants have discovered specific solvents and experimental conditions, producing a distinctly different polymorph form 2 loratadine . . . . This information stems from applicants' specification, but not from the cited prior art".).

D. Rejection of Claims 8-18 Under 35 U.S.C. § 112, First Paragraph

Claims 8-18 stand finally rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description and enablement requirements. According to the Examiner, there is a lack of description and enablement as to whether the particular form can be obtained in the claimed compositions.

Regarding written description, MPEP § 2163 states:

> An applicant shows possession of the claimed invention by describing the claimed invention with all its limitations. *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966. . . Limitations may not, however, be imported into the claims from the specification. (Emphasis added.)

Regarding enablement, MPEP § 2164.08 states:

> All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires the examiner determine exactly what subject matter is encompassed by the claims. (Emphasis added.)

The subject matter of claims 81-8 is directed to a composition comprising crystalline Form III of (S)-repaglinide. The claims contain no limitation requiring that the form be maintained indefinitely, or that it be the only form present, and Appellants submit that it is error to read such a limitation into the claims. The instant specification clearly describes and enables the preparation of compositions comprising crystalline Form III of (S)-repaglinide. (*See, e.g.*, instant specification, pages 15-16, ¶ 0056; pages 21-24, ¶¶ 0062-0073.) Furthermore, the specification clearly describes and enables methods for identifying and monitoring the crystalline form in the claimed compositions before, during and after their preparation. (*See, e.g.*, instant specification, page 16, ¶¶ 0053-0054; page 18, ¶ 0057)

Accordingly, Appellants submit that no case for lack of written description or enablement of claims 8-18 under § 112, first paragraph, has been made out, and the rejection should not be sustained.

CONCLUSION

Appellants submit that claims 1-2, 4-38, 40-48, 50, 51, 53, 54, 56, and 57 meet the requirements for patentability under §§ 102, 103 and 112. Accordingly, reversal of the Examiner's rejections is appropriate and is respectfully solicited.

Respectfully submitted,

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CLAIMS APPENDIX

1. A compound which is a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1.

2. The compound of claim 1, having an X-ray powder diffraction pattern, expressed in terms of 2 theta angles, that includes five or more peaks selected from the group consisting of 4.44 ± 0.09, 6.81 ± 0.09, 7.80 ± 0.09, 9.28 ± 0.09, 11.09 ± 0.09, 11.89 ± 0.09, 12.92 ± 0.09, 13.46 ± 0.09, 14.34 ± 0.09, 15.77 ± 0.09, 16.24 ± 0.09, 17.08 ± 0.09, 18.06 ± 0.09, 18.75 ± 0.09, 19.25 ± 0.09, 19.59 ± 0.09, 19.99 ± 0.09, 20.34 ± 0.09, 21.18 ± 0.09, 21.96 ± 0.09, 22.18 ± 0.09, 22.58 ± 0.09, 23.24 ± 0.09, 23.77 ± 0.09, 24.08 ± 0.09, 25.02 ± 0.09, 25.31 ± 0.09, 25.78 ± 0.09, 26.67 ± 0.09, 27.39 ± 0.09, 28.03 ± 0.09, 30.26 ± 0.09, 35.50 ± 0.09, and 38.74 ± 0.09 degrees.

4. The compound of claim 1, having a differential scanning calorimetry thermogram which exhibits a significant endotherm peak at about 80°C.

5. The compound of claim 4, having substantially the same differential scanning calorimetry thermogram as shown in Figure 2.

6. The compound of claim 1, having an infrared absorption spectrum with absorption bands at about 3291 cm^{-1}, about 3029 cm^{-1}, about 2935 cm^{-1}, about 2795 cm^{-1}, about 1292 cm^{-1}, about 1727 cm^{-1}, about 1643 cm^{-1}, about 1611 cm^{-1}, about 1537 cm^{-1}, about 1436 cm^{-1}, about 1225 cm^{-1}, about 1171 cm^{-1}, about

1087 cm^{-1}, about 1028 cm^{-1}, about 986 cm^{-1}, about 922 cm^{-1}, about 860 cm^{-1}, about 764 cm^{-1}, about 686 cm^{-1}, and about 533 cm^{-1}.

7. The compound of claim 6, having substantially the same infrared spectrum as that shown in Figure 3.

8. A composition comprising (S)-repaglinide as a solid, wherein at least 80% by weight of said solid (S)-repaglinide is in crystalline Form III, which has an X-ray powder diffraction pattern, expressed in terms of 2 theta angles, that includes five or more peaks selected from the group consisting of 4.44 ± 0.09, 6.81 ± 0.09, 7.80 ± 0.09, 9.28 ± 0.09, 11.09 ± 0.09, 11.89 ± 0.09, 12.92 ± 0.09, 13.46 ± 0.09, 14.34 ± 0.09, 15.77 ± 0.09, 16.24 ± 0.09, 17.08 ± 0.09, 18.06 ± 0.09, 18.75 ± 0.09, 19.25 ± 0.09, 19.59 ± 0.09, 19.99 ± 0.09, 20.34 ± 0.09, 21.18 ± 0.09, 21.96 ± 0.09, 22.18 ± 0.09, 22.58 ± 0.09, 23.24 ± 0.09, 23.77 ± 0.09, 24.08 ± 0.09, 25.02 ± 0.09, 25.31 ± 0.09, 25.78 ± 0.09, 26.67 ± 0.09, 27.39 ± 0.09, 28.03 ± 0.09, 30.26 ± 0.09, 35.50 ± 0.09, and 38.74 ± 0.09 degrees.

9. The composition of claim 8, wherein at least 90% by weight of said solid (S)-repaglinide is the crystalline Form III.

10. The composition of claim 8, wherein at least 95% by weight of said solid (S)-repaglinide is the crystalline Form III.

11. The composition of claim 8, wherein at least 99% by weight of said solid (S)-repaglinide is the crystalline Form III.

12. The composition of claim 8, wherein said solid (S)-repaglinide is substantially free of crystalline Forms I and II of (S)-repaglinide.

13. The composition of claim 8, wherein at least about 1% of said solid (S)-repaglinide is not crystalline Form III.

14. The composition of claim 8, wherein at least about 5% of said solid (S)-repaglinide is not crystalline Form III.

15. A pharmaceutical composition formed by combining:
a) a compound which is a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1; and
b) a pharmaceutically acceptable carrier or diluent.

16. The pharmaceutical composition of claim 15, further comprising one or more pharmaceutically acceptable excipients.

17. The pharmaceutical composition of claim 16, which is a solid dosage form for oral administration.

18. The pharmaceutical composition of claim 17, wherein said solid dosage form is a tablet.

19. A process for preparing a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1, said process comprising:
(a) providing a solution of (S)-repaglinide in a haloalkane solvent;

(b) contacting said solution with a C_5-C_{10} aliphatic or alicyclic hydrocarbon anti-solvent thereby forming a precipitate; and

(c) isolating the precipitate to provide the crystalline Form III of (S)-repaglinide.

20. The process of claim 19, further comprising drying the isolated precipitate.

21. The process of claim 19, wherein step (a) includes mixing a powder of (S)-repaglinide with the haloalkane solvent to form said solution.

22. The process of claim 21, wherein said powder of (S)-repaglinide is a solid form of (S)-repaglinide selected from the group consisting of crystalline Form I of (S)-repaglinide, crystalline Form II of (S)-repaglinide, and amorphous (S)-repaglinide.

23. The process of claim 19, wherein the haloalkane solvent is selected from the group consisting of dichloromethane, chloroform, and dichloroethane.

24. The process of claim 19, wherein the C_5-C_{10} aliphatic or alicyclic hydrocarbon anti-solvent is a C_5-C_7 aliphatic or alicyclic hydrocarbon.

25. The process of claim 19, wherein the C_5-C_{10} aliphatic or alicyclic hydrocarbon anti-solvent is selected from the group consisting of petroleum ether, hexane, n-heptane, cyclohexane, and cycloheptane.

26. The process of claim 19, wherein the concentration of said solution in step (a) is from about 0.25 gram to about 1 gram of (S)-repaglinide per milliliter of the haloalkane solvent.

27. The process of claim 19, wherein the concentration of said solution in step (a) is from about 0.4 gram to about 0.6 gram of (S)-repaglinide per milliliter of the haloalkane solvent.

28. The process of claim 19, wherein the concentration of said solution in step (a) is about 0.5 gram of (S)-repaglinide per milliliter of the haloalkane solvent.

29. The process of claim 19, wherein the ratio of said haloalkane to said C_5-C_{10} aliphatic or alicyclic hydrocarbon in step (b), measured volume-to-volume, ranges from about 1:1 to about 1:5, respectively.

30. The process of claim 19, wherein said ratio of said haloalkane to said C_5-C_{10} aliphatic or alicyclic hydrocarbon in step (b), measured volume-to-volume, is about 1:3, respectively.

31. The process of claim 19, wherein step (b) includes adding said C_5-C_{10} aliphatic or alicyclic hydrocarbon to said solution.

32. The process of claim 19, wherein said C_5-C_{10} aliphatic or alicyclic hydrocarbon anti-solvent is petroleum ether.

33. The process of claim 32, wherein said haloalkane is dichloromethane.

34. A compound which is the crystalline Form III of (S)-repaglinide produced by the process of claim 19.

35. A compound which is the crystalline Form III of (S)-repaglinide produced by the process of claim 33.

36. A process for preparing a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1, said process comprising:
(a) dissolving (S)-repaglinide in dichloromethane to form a solution;
(b) adding petroleum ether to the solution to form a precipitate; and
(c) isolating the precipitate to provide the crystalline Form III of (S)-repaglinide.

37. The process of claim 36, wherein the concentration in step (a) is from about 0.4 to about 0.6 gram of (S)-repaglinide per milliliter of dichloromethane, and the ratio of dichloromethane to petroleum ether in step (b), measured volume- to-volume, ranges from about 1:1 to about 1:5, respectively.

38. A compound which is an amorphous form of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 4.

40. A process for making an amorphous form of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 4, said process comprising:
(a) providing a solution of (S)-repaglinide in a lower alcohol;
(b) cooling said solution so that a solid mass separates; and
(c) isolating said separated solid mass to provide the amorphous form of (S)-repaglinide.

41. The process of claim 40, further comprising drying said isolated solid mass.

42. The process of claim 40, wherein step (a) includes mixing a powder of the (S)-repaglinide and the lower alcohol, and heating the mixture to a temperature of from about 35°C to about 70°C until the solution is formed.

43. The process of claim 42, wherein the mixture is heated to a temperature from about 45°C to about 55°C.

44. The process of claim 40, wherein the solution of (S)-repaglinide in step (b) is cooled to a temperature from about 0°C to about 5°C.

45. The process of claim 40, wherein the (S)-repaglinide in step (a) is selected from the group consisting of crystalline Form I of (S)-repaglinide, crystalline Form II of (S)-repaglinide, and crystalline Form III of (S)-repaglinide.

46. The process of claim 40, wherein the lower alcohol is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, and *t*-butanol.

47. The process of claim 40, wherein the lower alcohol is methanol.

48. A compound which is the amorphous form of (S)-repaglinide produced by the process of claim 40.

50. A process for preparing a crystalline Form II of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Table 3, said process comprising:

(a) providing a solution of (S)-repaglinide in an aromatic hydrocarbon solvent, with the proviso that said solvent does not include petroleum ether;

(b) cooling said solution to separate a solid mass; and

(c) isolating said solid mass to provide the crystalline Form II of (S)-repaglinide.

51. The process of claim 50, wherein said solvent in step (a) does not include any aliphatic hydrocarbon components.

53. The process of claim 50, wherein said aromatic hydrocarbon solvent in step (a) is selected from the group consisting of benzene, toluene, ethyl benzene, and xylene.

54. The process of claim 50, wherein said aromatic hydrocarbon solvent in step (a) is toluene.

56. The process of claim 50, wherein step (a) includes mixing a powder of (S)-repaglinide with the aromatic hydrocarbon solvent and heating said mixture to form the solution.

57. The process of claim 50, further comprising drying the isolated solid mass.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.